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Gulf War Veterans and Iraqi Nerve Agents at Khamisiyah: Postwar Hospitalization Data Revisited

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Chemical warfare agents were demolished by US soldiers at Khamisiyah, Iraq, in March 1991. The authors investigated postwar morbidity for Gulf War veterans, contrasting those who may have been exposed to low gaseous levels of nerve agents and those unlikely to have been exposed. Cox regression modeling was performed for hospitalizations from all causes and hospitalizations from diagnoses within 15 categories during the period March 10, 1991, through December 31, 2000, for the duration of active-duty status. After adjustment for all variables in the model, only two of 37 models suggested that personnel possibly exposed to subclinical doses of nerve agents might be at increased risk for hospitalization from circulatory diseases, specifically cardiac dysrhythmias. Of the 724 hospitalizations for cardiac dysrhythmias, 203 were in the potentially exposed group, slightly higher than expected (risk ratio = 1.23, 95% confidence interval: 1.04, 1.44). The increase was small in comparison with potential observational variability, but the findings are provocative and warrant further evaluation. Veterans possibly exposed to nerve agents released by the Khamisiyah demolition were not found to be at increased risk for hospitalizations from any other chronic diseases nearly 10 years after the Gulf War.

exposure, environmental; exposure, occupational; hospitalization; military medicine; morbidity; Persian Gulf syndrome; veterans

Abbreviations: CI, confidence interval; GIS, geographic information system; GPL, general population limit; ICD-9-CM, *International Classification of Diseases*, Ninth Revision, Clinical Modification; RR, risk ratio.

Throughout the 10 years following the Gulf War there has been much public and veteran concern that environmental exposures during the war were causing increased morbidity among Gulf War veterans. Research has focused on environmental exposures such as smoke from Kuwaiti oil well fires (1), ingestion of pyridostigmine bromide tablets (2), depleted uranium (3, 4), infectious diseases (5, 6), dust (7), and how these exposures and stressors may have resulted in multisymptom illnesses (8). Furthermore, investigations for associations between self-reported exposures and increased reporting of symptoms have not identified specific etiologies of illness (9–12). In addition to these efforts, there has been a great deal of focus on possible exposure to the chemical or

biological weapons that Iraq was known to possess during the Gulf War (13–16).

Although there is no evidence that Iraq used chemical weapons against coalition forces (17), the Department of Defense announced in June 1996 that the United Nations had found that chemical weapons were destroyed in March 1991 by US forces near Khamisiyah, Iraq. This prompted attempts to identify and notify those Gulf War veterans who might have been exposed to gaseous nerve agents in the hazard areas resulting from the demolition of chemical weapons at Khamisiyah. In a 1999 report (18), we compared the postwar hospitalization experience of these Gulf War veterans with that of other Gulf War veterans who were not likely to have been exposed. We found no evidence that Gulf War

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veterans, who were possibly exposed to nerve agents in the hazard areas identified by these original models, were suffering increased hospital morbidity through September 1995.

Since our report, exposure estimate models were greatly improved. In December 2000, the Office of the Special Assistant for Gulf War Illnesses released a much more detailed update (19) to its original 1997 case narrative (20). This work was followed by the final report in April 2002, identifying 101,752 Gulf War veterans as having been possibly exposed in the hazard areas created by the destruction of munitions at Khamisiyah (21). The revision of the meteorologic models, reduction in estimates of nerve agent released, combining of toxicity levels of both sarin and cyclosarin instead of only sarin, and inclusion of atmospheric removal mechanisms like deposition and degradation resulted in a greatly improved model of hazard areas. This model determined that a somewhat smaller geographic area of exposure was more likely than originally predicted. These new data, updated unit location and personnel data, and the addition of 5 years of hospitalization data for those veterans continuing in an activated capacity may allow better assessment of illnesses and chronic illnesses of those possibly exposed to chemical warfare agents in the Khamisiyah hazard areas in 1991. In this historical cohort study, we compared the postwar morbidity of 101,752 US military personnel possibly exposed to the revised nerve agent hazard areas at Khamisiyah, Iraq, in March 1991 with that of deployed personnel not likely to have been exposed.

MATERIALS AND METHODS

Study population

The study population consisted of 431,762 regular active-duty and Reserve, Army and Air Force personnel who were deployed to the Gulf War theater of operations for one or more days from August 8, 1990, through July 31, 1991, and who were in the theater of operations (22) during the time of the Khamisiyah demolition (March 1991). The analysis of postwar hospitalization data was limited primarily to regular active-duty military personnel, because active-duty personnel are rarely hospitalized outside the Department of Defense medical system (22, 23) and because Department of Defense automated hospitalization data were available for these personnel. Because Reserve and National Guard personnel are hospitalized in military facilities only while they are in an active-duty status, we included them in the analysis only while they were deployed. Reserve and National Guard personnel ($n = 84,690$) were excluded from the analyses after their estimated return to their civilian occupations (June 10, 1991).

Demographic and deployment data for Gulf War veterans established in 1997 were provided by the Defense Manpower Data Center, Monterey Bay, California, and reflected military status as of August 1, 1991. These data included age, marital status, gender, race/ethnicity (White, Black, Hispanic non-Black, and other), service branch (Army, Air Force), service type (active duty, National Guard, and Reserve), Department of Defense primary occu-

pational specialties (10 major categories, defined by the *DoD Occupational Conversion Manual*) (24), rank (enlisted, warrant officer, and commissioned officer), number of days in the Gulf theater (categorized by approximate quartiles as 1–107 days, 108–161 days, 162–202 days, 203–572 days), calendar period in the Gulf theater, salary, length of service, and date of separation from military service. The study was approved by the institutional review board of the Naval Health Research Center (San Diego, California), and it was conducted in compliance with all applicable federal regulations governing the protection of human subjects in research.

Hospitalization data

Hospitalization data for each service member included the date of admission and up to eight individual discharge diagnoses, captured from all Department of Defense hospitals during the period from August 1, 1989, through December 31, 2000. These data were linked to deployment and demographic data using a unique identifier. Diagnoses were coded according to the *International Classification of Diseases*, Ninth Revision, Clinical Modification (ICD-9-CM) (25). For analyses of major diagnostic categories, the decimal components of the ICD-9-CM diagnoses were not considered. As in previous reports (18, 22, 26, 27), a prewar hospitalization covariate was created and linked to denote hospitalization for any cause during the 12 months prior to August 1, 1990. Hospitalization data available from outside the Department of Defense health care system and outpatient data for the time period of this investigation were not available.

Meteorologic, transport, diffusion, and rocket destruction modeling

Since the 1997 Khamisiyah gaseous hazard area modeling, recommendations from a peer-review panel and the availability of new data and better modeling algorithms have guided the Office of Special Assistant for Gulf War Illnesses to make improvements in the Khamisiyah hazard area modeling (19, 21). The 2000 Khamisiyah gaseous hazard area modeling approach used the composite of four sets of modeling results to define a potential hazard area. Refinement to the modeling included a reduced estimate of 225 destroyed rockets containing nerve agent instead of 500, combined toxicity of sarin and cyclosarin where only sarin toxicity data were available in 1997, integration of atmospheric agent removal mechanisms including deposition (transfer of airborne material to the earth's surface) and degradation (decay), and refined meteorologic modeling methodologies.

Hazard area and exposure estimates

Exposure was defined by an existing health standard established by the Centers for Disease Control and Prevention of the Department of Health and Human Services. This standard is referred to as the "general population limit" (GPL). The Centers for Disease Control-recommended GPL is the maximum air concentration that anyone in the general population (including infants and elderly people) could be

exposed to continuously for 72 hours with no adverse effect (28). Additionally, the Centers for Disease Control states that even long-term exposure to these concentrations would not create any adverse health effects (19). Because potential Khamisiyah-related exposures were of much briefer duration, the GPL value was adjusted accordingly. Potential hazard areas were generated by the modeling using the 24-hour dosage derived from the adjusted-GPL-based concentration levels of 0.000003 mg/m^3 for sarin and 0.00001 mg/m^3 for cyclosarin (19).

Geographic information systems data

Geographic information system (GIS) techniques were used to plot revised military unit daily locations in the Gulf War theater. These data were provided by the US Armed Services Center for Unit Records Research, Springfield, Virginia, and were compiled and organized using relational database management system software (Oracle, Redwood Shores, California). Using Arc View GIS software (Environmental Systems Research Institute, Redlands, California), we geo-referenced the four individual gaseous hazard area models to derive daily hazard areas for the period from March 10 to March 13, 1991, by selecting the union of the composite areas. These daily hazard areas were geo-referenced with respective daily troop location data to determine which units were possibly exposed. To associate individual personnel from the units found within the hazard areas, we cross-matched troop unit identification codes to an updated Defense Manpower Data Center Desert Shield/Desert Storm personnel file.

Study outcomes

As in the previous report (18), we chose to examine broad outcomes for our analyses, including hospitalizations for any cause and hospitalizations due to diagnoses in 15 major ICD-9-CM categories (25). In addition to the 15 broad outcomes of hospitalization, specific diagnoses, suggested by an expert panel as possible chronic manifestations of acute subclinical nerve agent exposure, were examined to avoid missing a risk difference due to the possible masking effect of aggregated ICD-9-CM diagnoses (29). Additionally, we planned to investigate the 10 most frequent specific three-digit diagnoses within any broad category for which veterans were at increased risk of hospitalization.

Statistical analyses

Hospitalizations were sorted in chronologic order, and diagnostic fields were scanned in numerical order for ICD-9-CM diagnoses of interest. Univariate analyses were performed to assess possible associations between demographic, exposure, and deployment variables and any-cause hospitalization. An exploratory model analysis was developed to further assess significant risk factor associations, while simultaneously adjusting for all influential predictors of the targeted outcome. These analyses yielded a consistent set of influential covariates, with p values of 0.15 or below, that were then included in subsequent model analyses. Using

regression diagnostics, we investigated the collinearity and multiplicative interaction among variables. We used Cox's proportional hazards time-to-event modeling to compare the Department of Defense hospitalization experience of Gulf War veterans, while accounting for separation from military service over the nearly 10-year period. Subjects were classified as having an event if they were hospitalized in any Department of Defense hospital worldwide with any of the targeted outcomes. Follow-up time for the modeling of a single event was calculated from March 10, 1991, until hospitalization, separation from active-duty military service, or December 31, 2000, whichever occurred first. Because no separation data were available for Reserve personnel, they were assumed to have remained in active service until June 10, 1991, at which time most Reservists had returned to civilian careers. Additionally, to investigate rare events occurring among specific diagnoses, we also developed Poisson models to estimate the risk ratio of hospitalization with the rare event.

Modeling multiple hospitalizations within each major ICD-9-CM diagnostic category was accomplished by using a marginal regression model with a conditional method proposed by Prentice et al. (30) and Therneau and Grambsch (31). Follow-up time for multiple hospitalization modeling was calculated from March 10, 1991, and subsequent hospital admission dates to first or subsequent hospitalization, separation from active-duty military service, or December 31, 2000, whichever occurred first.

Using SAS software (version 8.0; SAS Institute, Inc., Cary, North Carolina), we calculated risk ratios and 95 percent confidence intervals for the 418,072 personnel with complete covariate data (32). The time-to-first-event estimates were calculated by exposure status, allowing computation and graphing of the cumulative probability of hospitalization as a function of time.

RESULTS

Chemical warfare agents were present at Khamisiyah, Iraq, during demolitions by US soldiers in March 1991. Many of the rockets containing these chemical warfare agents were destroyed by US soldiers along with the large cache of Iraqi weapons that were stored at the munitions depot. Subsequently, almost 102,000 Army and Air Force personnel were identified as possibly exposed to low-dose levels of nerve agents. However, no records were found of service members who reported at the time to be suffering acute symptoms, such as rhinorrhea, muscle twitching, chest tightness, or headache (19, 33, 34). Demographic and exposure data were complete and available for 418,072 (96.8 percent) of the 431,762 Army and Air Force Gulf War veterans (table 1). These included 333,382 (79.7 percent) regular active-duty and 84,690 (20.3 percent) Reserve and National Guard personnel; 99,614 were considered possibly exposed, and 318,458 were considered not exposed to Khamisiyah hazard areas.

Univariate analyses identified the following predictors of any postwar hospitalization: Khamisiyah hazard area exposure status, age group, marital status, service type, gender, occupational category, race/ethnicity, pay grade, salary,

TABLE 1. Characteristics* of US Gulf War veterans possibly exposed to nerve agents released by the Khamisiyah demolition in March 1991

Variable	Possibly exposed		Nonexposed	
	No.	%	No.	%
Attrition				
No separation from military service	42,584	42.7	134,060	42.1
Separation during follow-up	57,030	57.3	184,398	57.9
Gender				
Male	89,067	89.4	290,293	91.2
Female	10,547	10.6	28,165	8.8
Age (years)				
17-22	28,762	28.9	86,014	27.0
23-26	24,034	24.1	76,945	24.2
27-32	22,398	22.5	78,310	24.6
33-65	24,420	24.5	77,189	24.2
Status				
Active duty	76,497	76.8	256,885	80.7
Reserve	23,117	23.2	61,573	19.3
Prewar hospitalization				
No	93,419	93.8	297,815	93.5
Yes	6,195	6.2	20,643	6.5
Military pay grade				
Commissioned officer	9,864	9.9	33,389	10.5
Warrant officer	1,832	1.8	5,299	1.7
Enlisted	87,918	88.3	279,770	87.9
Race/ethnicity				
White	62,703	63.0	214,526	67.4
Black	28,484	28.6	80,536	25.3
Hispanic	3,363	3.4	9,366	2.9
Other	5,064	5.1	14,030	4.4
Branch of service				
Air Force	1,227	1.2	75,723	23.8
Army	98,387	98.8	242,735	76.2
No. of days deployed to theater				
1-107	15,618	15.7	86,845	27.3
108-161	30,789	30.9	73,295	23.0
162-202	24,112	24.2	82,200	25.8
203-572	29,095	29.2	76,118	23.9
Marital status				
Single or divorced	45,859	46.0	138,976	43.6
Married	53,755	54.0	179,482	56.4
Occupational category				
Infantry, gun crews, and seamanship	23,028	23.1	75,299	23.6
Electronic equipment repairers	5,131	5.2	19,281	6.1
Communications and intelligence	9,845	9.9	30,976	9.7
Health care	8,159	8.2	23,783	7.5
Photography	2,554	2.6	8,579	2.7
Functional support	14,728	14.8	41,002	12.9
Electrical/mechanical equipment repair	14,623	14.7	60,576	19.0
Craft workers	2,987	3.0	9,599	3.0
Service and supply handlers	17,260	17.3	45,696	14.4
Nonoccupational and missing	1,299	1.3	3,667	1.2

* Reflect possibly exposed and nonexposed Gulf War veterans with complete covariate data and who were on active service at the time of the Khamisiyah demolition.

TABLE 2. Adjusted risk ratios for any cause postwar hospitalization among Army and Air Force active duty and Reserve* Gulf War veterans in US Department of Defense hospitals, March 10, 1991, to December 31, 2000

Variable	No.	%	% hospitalized	RR†,‡	95% CI†	RR†,§	95% CI
Exposure to Khamisiyah hazard area							
Nonexposed¶	318,458	76.2	18.8				
Exposed	99,614	23.8	18.4	1.07	1.05, 1.09	0.99	0.98, 1.01
Gender							
Male¶	379,360	90.7	18.2				
Female	38,712	9.3	23.0	1.61	1.58, 1.65	1.57	1.53, 1.61
Age (years)							
17-22¶	114,776	27.4	17.4				
23-26	100,979	24.2	17.9	0.90	0.89, 0.92	0.97	0.95, 0.99
27-32	100,708	24.1	20.5	0.92	0.90, 0.94	1.02	1.00, 1.04
33-65	101,609	24.3	19.2	1.15	1.12, 1.17	1.29	1.26, 1.32
Status							
Active duty¶	333,382	79.7	22.8				
Reserve	84,690	20.3	2.7	1.45	1.38, 1.52	1.33	1.27, 1.40
Prewar hospitalization							
No¶	391,234	93.6	17.9				
Yes	26,838	6.4	29.9	1.70	1.66, 1.74	1.64	1.60, 1.68
Military pay grade							
Commissioned officer¶	43,253	10.4	17.0				
Warrant officer	7,131	1.7	24.6	1.35	1.28, 1.42	1.26	1.19, 1.33
Enlisted	367,688	87.9	18.8	1.40	1.37, 1.43	1.52	1.49, 1.57
Race/ethnicity							
White¶	277,229	66.3	17.9				
Black	109,020	26.1	20.6	1.05	1.03, 1.06	0.92	0.91, 0.94
Hispanic	12,729	3.0	20.3	0.97	0.94, 1.01	0.89	0.86, 0.93
Other	19,094	4.6	17.9	1.00	0.97, 1.04	0.93	0.89, 0.96
Branch of service							
Air Force¶	76,950	18.4	18.7				
Army	341,122	81.6	18.7	1.33	1.30, 1.35	1.32	1.29, 1.34
No. of days deployed to theater							
1-107¶	102,463	24.5	18.2				
108-161	104,084	24.9	15.6	0.96	0.94, 0.98	0.92	0.91, 0.94
162-202	106,312	25.4	19.3	0.98	0.96, 1.00	0.98	0.96, 1.00
203-572	105,213	25.2	21.7	1.04	1.02, 1.06	1.01	0.99, 1.03
Marital status							
Single or divorced¶	184,835	44.2	16.5				
Married	233,237	55.8	20.4	1.01	1.00, 1.03	1.02	1.00, 1.04
Occupational category							
Infantry, gun crews, and seamanship¶	98,327	23.5	20.0				
Electronic equipment repairers	24,412	5.8	19.6	1.06	1.03, 1.10	1.08	1.05, 1.11
Communications and intelligence	40,821	9.8	20.5	1.13	1.09, 1.17	1.02	0.98, 1.06
Health care	31,942	7.6	18.3	1.52	1.47, 1.58	1.33	1.28, 1.38
Photography	11,133	2.7	20.1	1.18	1.12, 1.24	1.07	1.02, 1.13
Functional support	55,730	13.3	19.6	1.20	1.16, 1.25	1.02	0.99, 1.06
Electrical/mechanical equipment repair	75,199	18.0	18.7	1.08	1.04, 1.11	1.03	1.00, 1.06
Craft workers	12,586	3.0	16.9	1.21	1.15, 1.28	1.16	1.10, 1.22
Service and supply handlers	62,956	15.1	14.9	1.22	1.17, 1.26	1.10	1.06, 1.14
Nonoccupational and missing	4,966	1.2	14.3	1.14	1.05, 1.23	1.14	1.05, 1.24

* Only until June 10, 1991.

† RR, risk ratio based on a single event accounting for time; CI, confidence interval.

‡ Unadjusted for other variables.

§ Adjusted for all other variables.

¶ A reference category.

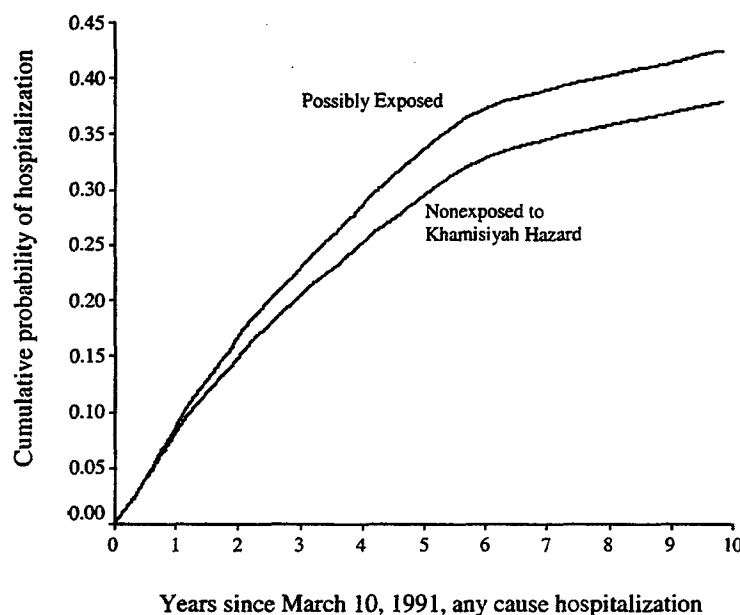


FIGURE 1. Cumulative probability of postwar hospitalization for any cause in US Department of Defense hospitals, March 10, 1991, to December 31, 2000, among regular active-duty and Reserve, Army and Air Force, Gulf War veterans.

length of service, calendar period in the Gulf theater, number of days in the Gulf theater, and prewar hospitalization. Regression diagnostics revealed that the following pairs of variables were collinear: 1) age and length of service and 2) salary and pay grade. Due to this collinearity, salary and length of service were removed from further modeling. Personnel with missing occupational data were found to be similar in outcomes to those with an undesignated occupational category, so these groups were combined.

During the nearly 10-year observation period, 18.4 percent of the exposed personnel were hospitalized, and 18.8 percent of nonexposed personnel were hospitalized. Attrition was approximately equal, with 57.3 percent of the exposed personnel and 57.9 percent of the nonexposed personnel separating from military service over the nearly 10-year period. The adjusted risk of any-cause hospitalization for exposed veterans was not significantly different from the risk for the nonexposed veterans. However, gender, age, military pay grade, Reserve or National Guard status, race/ethnicity, prewar hospitalization, and occupational category remained statistically associated with hospitalization for any cause (table 2). The corresponding cumulative probability of hospitalization plots for exposed personnel versus nonexposed personnel remained very stable and nearly parallel over the 10-year follow-up period (figure 1).

Cox's proportional hazard modeling was completed for the first hospitalization for each of the 15 major ICD-9-CM categories. With "nonexposed" as the referent group, only the category of diseases of the circulatory system showed a significant association with exposure after adjusting for all other variables in the model (risk ratio (RR) = 1.07, 95 percent confidence interval (CI): 1.01, 1.13) (figure 2). Additionally, to account for as little as 8 percent of the

personnel's being hospitalized more than once in the category of skin diseases and as much as 32.8 percent of the personnel's being hospitalized more than once in the category of complications of pregnancy during the nearly 10-year period, Cox's proportional hazard modeling was extended to model multiple hospitalizations for each of the 15 major ICD-9-CM categories. These models produced similar results to the first event modeling, with only the category of diseases of the circulatory system significantly associated with possible exposure after adjusting for all other variables in the model (RR = 1.10, 95 percent CI: 1.05, 1.16) (table 3). The 10 most frequent diagnoses within the category of diseases of the circulatory system were essential hypertension, hemorrhoids, cardiac dysrhythmias, chronic ischemic heart disease, varicose veins of other sites, varicose veins of lower extremities, acute myocardial infarction, other diseases of the endocardium, conduction disorders, and other venous embolism and thrombosis (table 4). Of these 10 diagnoses, modeling time until first hospitalization found only cardiac dysrhythmias to be significantly associated with possible exposure after adjusting for all other variables in the model (RR = 1.22, 95 percent CI: 1.02, 1.45) (figure 3).

Additional modeling for specific diagnoses revealed slight positive and negative risk ratios; however, none of these associations was statistically significant (table 5). Additional Poisson modeling of rare events estimated similar risk to that of the Cox modeling. Again, these associations were not found to be statistically significant.

DISCUSSION

In March 1991, during the final days of one of the briefest full-scale military conflicts in US history, US troops deto-

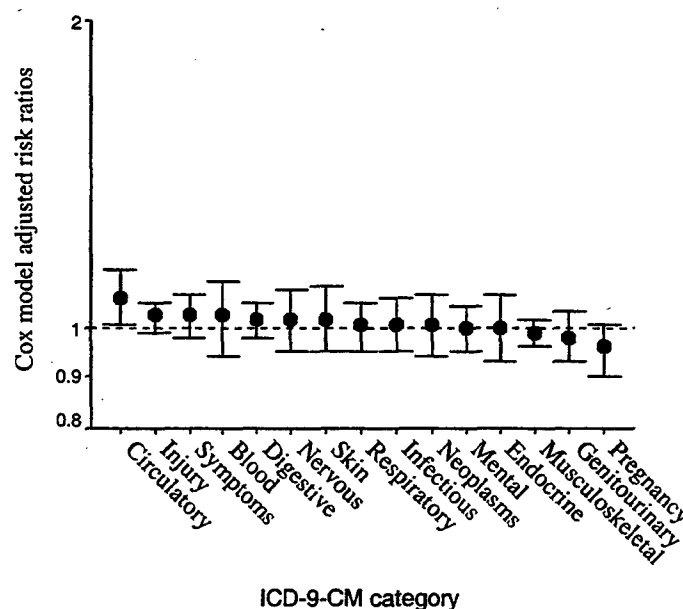


FIGURE 2. Adjusted risk ratios and 95% confidence intervals for possibly exposed versus nonexposed US veterans experiencing hospitalization for one of the 15 major *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM), categories from March 10, 1991, to December 31, 2000.

nated large munitions caches in southern Iraq. One of these sites, a large depot at Khamisiyah, Iraq, was later shown to contain rockets armed with the nerve agents sarin and cyclosarin. Although there is no evidence that Iraq used

chemical or biological weapons during the Gulf War (17), public and veteran concern mounted over possible adverse health effects among those possibly exposed to the munitions destruction at Khamisiyah. The potential acute and

TABLE 3. Multiple post-Gulf War hospitalizations by major three-digit ICD-9-CM* categories for follow-up among US veterans, March 10, 1991, to December 31, 2000†

ICD-9-CM codes	Major diagnostic categories	Exposed (n = 99,614)		Nonexposed (n = 318,458)		RR*	95% CI*
		One event (%)	Two or more events (%)	One event (%)	Two or more events (%)		
001-139	Infection and parasitic	89.0	11.0	88.3	11.7	0.99	0.94, 1.04
140-239	Neoplasms	82.7	17.3	81.8	18.2	0.97	0.91, 1.03
240-279	Endocrine, nutritional, and metabolic diseases	84.2	15.8	85.0	15.0	1.00	0.94, 1.06
280-289	Blood diseases	85.8	14.2	85.5	14.5	0.96	0.89, 1.03
290-319	Mental disorders	74.8	25.2	73.6	26.4	1.02	0.97, 1.06
320-389	Nervous system diseases	78.9	21.1	79.7	20.4	1.02	0.97, 1.08
390-459	Circulatory system diseases	73.8	26.2	76.1	23.9	1.10	1.05, 1.16
460-519	Respiratory system diseases	86.1	13.9	86.3	13.7	0.99	0.95, 1.04
520-579	Digestive system diseases	83.4	16.6	83.5	16.5	1.01	0.98, 1.04
580-629	Genitourinary system diseases	80.4	19.6	81.1	18.9	0.96	0.91-1.00
630-676	Complications of pregnancy	67.2	32.8	64.5	35.5	0.94	0.90, 0.99
680-709	Skin diseases	91.9	8.1	91.0	9.0	1.01	0.94, 1.09
710-739	Musculoskeletal system diseases	76.2	23.8	76.6	23.4	0.99	0.96, 1.02
780-799	Symptoms, signs, ill-defined	83.4	16.6	84.6	15.4	1.04	1.00, 1.09
800-999	Injury and poisoning	85.9	14.1	86.5	13.5	1.02	0.99, 1.06

* ICD-9-CM, *International Classification of Diseases*, Ninth Edition, Clinical Modification; RR, adjusted risk ratio based on one or more hospitalizations in a specific diagnostic category; CI, confidence interval.

† Percentages are calculated on the basis of personnel's having at least one hospitalization.

TABLE 4. Adjusted risk ratios for post-Gulf War hospitalizations due to the 10 most frequent three-digit diagnoses within the category of diseases of the circulatory system, March 10, 1991, to December 31, 2000

ICD-9-CM* codes	Specific diagnoses	Exposed (n = 99,614)	Nonexposed (n = 318,458)	RR*	95% CI*
401	Essential hypertension	643	1,793	1.06	0.97, 1.16
455	Hemorrhoids	287	881	1.02	0.89, 1.18
427	Cardiac dysrhythmias	203	571	1.23	1.04, 1.44
414	Other forms of chronic ischemic heart disease	162	418	1.19	0.98, 1.43
456	Varicose veins of other sites	118	375	1.14	0.93, 1.41
410	Acute myocardial infarction	73	192	1.20	0.90, 1.58
454	Varicose veins of lower extremities	68	254	0.82	0.63, 1.08
424	Other diseases of endocardium	70	198	1.15	0.87, 1.52
453	Other venous embolism and thrombosis	53	149	1.05	0.76, 1.44
426	Conduction disorders	49	170	1.00	0.73, 1.37

* ICD-9-CM, *International Classification of Diseases*, Ninth Edition, Clinical Modification; RR, adjusted risk ratio; CI, confidence interval.

long-term health effects of exposure to sarin and cyclosarin have been reviewed previously (17, 18, 35, 36). Although researchers have studied the effects of low-level exposure to anticholinesterases (37) and the health consequences associated with high-, intermediate-, and low-level exposures to organophosphate nerve agents (38), data are sparse regarding the long-term effects of exposure to subclinical doses of sarin or cyclosarin in humans.

As part of our continuing efforts to assess plausible relations among potential Gulf War exposures and health outcomes, we examined the hospitalization experience of US military personnel who were possibly exposed to the refined hazard area estimates after the destruction of chemical munitions at Khamisiyah, Iraq. In this follow-up report, the possibly exposed included more than 35,000 personnel who were not within the GPL hazard areas in the 1997 modeling (21). Furthermore, the additional 5 years of follow-up have allowed development of models to account for multiple hospitalizations or late-occurring diagnoses over the study period.

These exposure-outcome relations were evaluated using updated electronic Department of Defense databases containing deployment history, service, demographic information, hospitalization, daily troop unit location, meteorologic hazard area modeling, and dispersion modeling data. As in previous reports, personnel who were generally older,

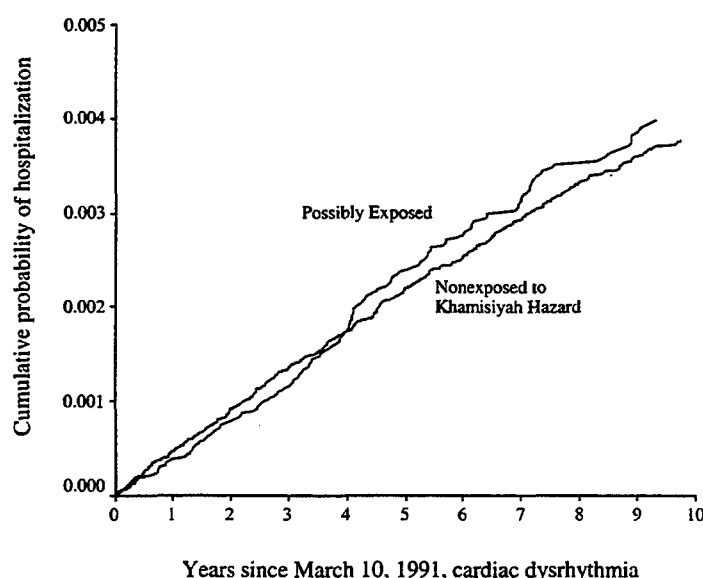


FIGURE 3. Cumulative probability of postwar hospitalization for cardiac dysrhythmias in US Department of Defense hospitals, March 10, 1991, to December 31, 2000, among regular active-duty and Reserve, Army and Air Force, Gulf War veterans.

TABLE 5. Adjusted risk ratios for post-Gulf War hospitalizations due to selected diagnoses, in US Department of Defense hospitals, thought to be manifestations of chemical munitions hazard area exposure, March 10, 1991, to December 31, 2000

ICD-9-CM* codes	Specific diagnoses	Exposed (n = 99,614)	Nonexposed (n = 318,458)	RR*,†	95% CI*	RR‡	95% CI
354	Mononeuritis of upper limb	188	578	1.06	0.90, 1.26		
355	Mononeuritis of lower limb	133	396	1.05	0.85, 1.28		
356	Hereditary and idiopathic peripheral neuropathy	11	47	0.72	0.37, 1.39	0.72	0.37, 1.40
357	Inflammatory and toxic neuropathy	9	23	1.34	0.62, 2.90	1.36	0.63, 2.94
358	Myoneural disorders	7	13	1.93	0.77, 4.85	1.92	0.78, 4.83
359	Muscular dystrophies and other myopathies	6	17	1.25	0.49, 3.18	1.25	0.49, 3.17
All	All of the above diagnoses	341	1,048	1.04	0.92, 1.18		

* ICD-9-CM, *International Classification of Diseases*, Ninth Edition, Clinical Modification; RR, risk ratio; CI, confidence interval.

† Cox regression adjusted risk ratio.

‡ Poisson regression adjusted risk ratio.

enlisted, female, persons who were hospitalized before the war, and health care workers were at increased risk of hospitalization for any cause after the war (22).

From the 37 risk-factor models, it is interesting that Gulf War veterans who were possibly exposed to subclinical doses of nerve agent were at slightly increased risk for both single and multiple postwar hospitalizations due to circulatory system diagnoses, specifically cardiac dysrhythmias. Cardiac dysrhythmias are abnormal rates or rhythms of the heart related to a disruption of the normal functioning of the electrical conduction system of the heart. Further investigation showed that the majority of these cases were specific diagnoses of atrial fibrillation (ICD-9-CM code 427.31) and other specified cardiac dysrhythmias (ICD-9-CM code 427.89), including coronary sinus, ectopic, and nodal rhythm disorders. Although a war setting might be conducive to acute disturbances of the rhythm of the heart, there was no evidence of such a deployment effect upon postwar hospitalizations with circulatory disease when all Gulf War veterans were compared with nondeployed veterans using Department of Defense, Department of Veterans Affairs, and California hospitalization data (22, 39). Similarly, Gulf War veterans appear to bear a lower risk for circulatory hospitalizations than do Vietnam veterans (40).

Circulatory system diagnoses, specifically cardiac dysrhythmia, have not been frequent diagnoses in Gulf War veteran health registry evaluations (41–43), nor have these diagnoses been the subject of frequent self-report among Gulf War veteran studies (11, 44). However, the Goss Gilroy health study of 3,000 Canadian Gulf War veterans found an increased prevalence (4.7 percent) of self-reported circulatory problems when compared with controls (1.8 percent) (45). Furthermore, the only Gulf War veteran study in which the authors found indications that Gulf War veterans were specifically experiencing irregular heart rates was a modest cross-sectional survey of 300 Gulf War era veterans (8). In this survey, Proctor et al. found that two US Gulf War veteran cohorts were at increased odds of reporting “irregular heart beats” or “heart fluttering” (odds ratios = 2.4 and 4.1) and “racing heart” (odds ratios = 1.8 and 3.0) compared with Germany-deployed US veterans.

Other non-Gulf War-related studies focusing on the effects of organophosphate compounds have reported similar findings. A study of victims of the 1995 Tokyo sarin attack who were followed for 3 years found an initial proportion of 9.5 percent with the symptom “sudden palpitations” that decreased to 8.7 percent and 6.3 percent over subsequent years of observation (46). Jones et al. (47) found that, of 1,856 British servicemen with postcombat syndromes, the sixth most frequent symptom was “rapid or irregular heartbeat” and that functional cardiac disorders were frequent in soldiers fighting in the Boer War and World War I. An animal study investigating organophosphate compounds demonstrated that high concentrations of the compounds, such as sarin, bind to the A1 adenosine receptors in ovine cardiac membranes and suggested that these compounds affect the mechanical responses of the heart (48). Further research, including more animal studies, may be justified in order to establish a biologic mechanism and to better validate these findings.

The present study’s findings of an adjusted association between possible exposure to Khamisiyah hazard areas and cardiac dysrhythmias are based on a low magnitude of effect (RR = 1.22, 95 percent CI: 1.02, 1.45) and might be due to chance alone. Our study had a number of important limitations. Acquiring reliable exposure estimates and projecting them on personnel to obtain exposure data at the individual level is very challenging. Ascertainment of quantitative estimates of other potentially confounding behavioral and environmental exposures, such as tobacco use, diesel exhaust, combustion of jet fuel, and other weapons depots that may have contained chemical weapons, was not possible for each individual. The limitations of epidemiologic studies that use group exposure data and individual outcome data without accounting for other possible confounding exposures have been discussed previously (18, 49, 50).

Further limitations include the choice of hospitalization as the measure of health effect. This limited the analyses to morbidity severe enough to require admission to a Department of Defense hospital for inpatient care. Outpatient data and data from personnel who sought private care outside the Department of Defense while on active duty were not available,

diminishing the ability for examination of the full spectrum of health effects. However, in an investigation of 3,831 Gulf War Seabees, the authors report no association between Khamisiyah hazard area exposure and self-reported symptom morbidity (9). Additionally, hospitalization data were available for only active and Reserve Gulf War veterans who remained on active duty or retired with medical benefits after the end of the war. This limitation may be mitigated by the facts that additional analyses were conducted after removing Reservists from the modeling and the findings remain essentially unchanged, that attritions between exposed and nonexposed veterans were found to be similar over the nearly 10-year follow-up, and that the mean follow-up time for those exposed was 2.9 person-years and for those nonexposed was 3.2 person-years. Furthermore, although the distributions of demographic variables over exposure status were similar, it is possible that those personnel in direct combat roles, as a group, were more physically fit than support personnel and thus less likely to be hospitalized post-deployment. Finally, the observation period of nearly 10 years may not be long enough for all possible long-term sarin and cyclosarin health effects to manifest.

Despite limitations, our study has a number of unique characteristics that may strengthen its conclusions. Sophisticated meteorologic and dispersion modeling techniques were integrated along with testimony by witnesses and GIS unit tracking to identify those possibly exposed to the gaseous hazard areas. Hospitalization outcome data are very complete for active-duty military personnel who seldom seek care outside the Department of Defense health care system (22, 23), and they reflect a more objective measure than self-reported symptoms or illnesses. Additionally, being able to analyze single, uncorrelated events as well as multiple events by using the Cox model permitted the examination of all event information. Finally, our large study population permitted robust risk estimates and considerable statistical power to detect even small differences in hospitalization risk across exposure and demographic groups, making it very likely that if true differences in hospitalization risk existed between exposed and nonexposed veterans, we would have detected them.

In summary, the use of refined exposure estimates to identify those possibly exposed to Khamisiyah nerve agent hazard areas in the Gulf War does not support the hypothesis that such personnel were generally at increased risk of hospitalization after the war. Investigation of both broad and specific outcomes, however, resulted in the finding of a small, increased association with circulatory system disorders, specifically cardiac dysrhythmia, among the possibly exposed personnel. Future work to explore this association may include toxicologic modeling in animals, epidemiologic case-control studies, and prospective evaluations in large military populations such as the Millennium Cohort (51). Our findings of no other increased risk for the remaining 14 categories and specific diagnoses are, however, consistent with the previous report and other studies of health outcomes following military service in the Gulf War. These findings, in addition to a report noting no increase in mortality for the possibly exposed (52), may be reassuring to those veterans concerned about other health effects associated with possible exposure to munitions destruction at Khamisiyah, Iraq.

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14. ABSTRACT (maximum 200 words)

The authors sought to determine if the destruction of munitions during the Gulf War, and presumed subclinical nerve agent exposures in Gulf War veterans, was associated with increased postwar morbidity. Using nerve agent exposure modeling estimates, the hospitalization experience of possibly exposed Gulf War veterans was compared with that of other Gulf War veterans who were deployed to the region but not likely exposed. Exposure and demographic data were available for 418,072 (96.8%) Army and Air Force Gulf War veterans. Cox regression modeling was performed for hospitalizations from all causes and hospitalizations from diagnoses within 15 categories during the period March 10, 1991, to January 31, 1999. Two of thirty-seven models indicated that personnel possibly exposed to subclinical doses of nerve agent were at increased risk for hospitalization from circulatory diseases, specifically cardiac dysrhythmias. Although the relative risk of hospitalization for dysrhythmias was small (RR = 1.22; 95% CI, 1.02, 1.45) and may be due to chance alone, the findings are provocative and warrant further evaluation. Veterans possibly exposed to nerve agents in Khamisiyah, Iraq, were not found to be at increased risk for hospitalizations from any other chronic diseases nearly 10 years after the Gulf War.

14. SUBJECT TERMS

exposure, environmental; exposure, occupational; hospitalization; military medicine; morbidity; Persian Gulf Syndrome, veterans

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